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Filed: 03/07/2001
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Amendments to the Claims:

The listing of claims will replace all prior versions, and listings, of the claims in the application:

Listing of Claims

Claims 1-25 (Cancelled).

26. (Currently Amended) A method for lowering levels of one or more serum lipids in a patient, ~~said method~~ comprising: administering to a patient in need **thereof** ~~having one or more serum lipid levels lowered~~ a lipid-lowering effective amount of a GLP-1 agonist, wherein said GLP-1 agonist is selected from the group consisting of GLP-1 (7-37), GLP-1 (7-36) amide, ~~exendin-3, exendin-4,~~ or an analogue or derivative of any of the foregoing, **wherein the patient in need thereof is not receiving insulin treatment and the one or more serum lipids are selected from the group consisting of: triglycerides and free fatty acids;[[.]]**

the GLP-1 derivative is a GLP-1 derivative of formula I:

7 8 9 10 11 12 13 14 15 16 17
His-Xaa-Xaa-Gly-Xaa-Phe-Thr-Xaa-Asp-Xaa-Xaa-

18 19 20 21 22 23 24 25 26 27 28
Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Phe-

29 30 31 32 33 34 35 36 37 38
Ile-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa

39 40 41 42 43 44 45
Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa

(I)

wherein

Xaa at position 8 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, Met, or Lys,

Xaa at position 9 is Glu, Asp, or Lys,

Xaa at position 11 is Thr, Ala, Gly, Ser, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 14 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 16 is Val, Ala, Gly, Ser, Thr, Leu, Ile, Tyr, Glu, Asp, or Lys,

Xaa at position 17 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 18 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 19 is Tyr, Phe, Trp, Glu, Asp, or Lys,

Xaa at position 20 is Leu, Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 21 is Glu, Asp, or Lys,

Xaa at position 22 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 23 is Gln, Asn, Arg, Glu, Asp, or Lys,

Xaa at position 24 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Arg, Glu, Asp, or Lys,

Xaa at position 25 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 26 is Lys, Arg, Gln, Glu, Asp, or His,

Xaa at position 27 is Glu, Asp, or Lys,

Xaa at position 30 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 31 is Trp, Phe, Tyr, Glu, Asp, or Lys,

Xaa at position 32 is Leu, Gly, Ala, Ser, Thr, Ile, Val, Glu, Asp, or Lys,

Xaa at position 33 is Val, Gly, Ala, Ser, Thr, Leu, Ile, Glu, Asp, or Lys,

Xaa at position 34 is Lys, Arg, Glu, Asp, or His,

Xaa at position 35 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 36 is Arg, Lys, Glu, Asp, or His,

Xaa at position 37 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys, or is deleted,

Xaa at position 38 is Arg, Lys, Glu, Asp, or His, or is deleted,

Xaa at position 39 is Arg, Lys, Glu, Asp, or His, or is deleted,

Xaa at position 40 is Asp, Glu, or Lys, or is deleted,

Xaa at position 41 is Phe, Trp, Tyr, Glu, Asp, or Lys, or is deleted,

Xaa at position 42 is Pro, Lys, Glu, or Asp, or is deleted,

Xaa at position 43 is Glu, Asp, or Lys, or is deleted,

Xaa at position 44 is Glu, Asp, or Lys, or is deleted, and

Xaa at position 45 is Val, Glu, Asp, or Lys, or is deleted, or

(a) a C_{1-6}-ester thereof,

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(b) an amide, C_{1-6}-alkylamide, or C_{1-6}-dialkylamide thereof; or

(c) a pharmaceutically acceptable salt thereof,

provided that

(i) when the amino acid at position 37, 38, 39, 40, 41, 42, 43 or 44 is deleted, then each amino acid downstream of the amino acid is also deleted,

(ii) the derivative of the GLP-1 analog contains only one or two Lys,

(iii) the ε-amino group of one or both Lys is substituted with a lipophilic substituent optionally via a spacer;

the GLP-1 analogue has the formula II:

7 8 9 10 11 12 13 14 15 16 17
His-Xaa-Xaa-Gly-Xaa-Phe-Thr-Xaa-Asp-Xaa-Xaa-

18 19 20 21 22 23 24 25 26 27 28
Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Phe-

29 30 31 32 33 34 35 36 37 38
Ile-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa

39 40 41 42 43 44 45
Xaa-Xaa-Xaa-Xaa-Xaa-Xaa-Xaa

(II)

wherein

Xaa at position 8 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, Met, or Lys,

Xaa at position 9 is Glu, Asp, or Lys,

Xaa at position 11 is Thr, Ala, Gly, Ser, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 14 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 16 is Val, Ala, Gly, Ser, Thr, Leu, Ile, Tyr, Glu, Asp, or Lys,

Xaa at position 17 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 18 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 19 is Tyr, Phe, Trp, Glu, Asp, or Lys,

Xaa at position 20 is Leu, Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 21 is Glu, Asp, or Lys,

Xaa at position 22 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 23 is Glu, Asn, Arg, Glu, Asp, or Lys,

Xaa at position 24 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Arg, Glu, Asp, or Lys,

Xaa at position 25 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 26 is Lys, Arg, Gln, Glu, Asp, or His,

Xaa at position 27 is Glu, Asp, or Lys,

Xaa at position 30 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 31 is Trp, Phe, Tyr, Glu, Asp, or Lys,

Xaa at position 32 is Leu, Gly, Ala, Ser, Thr, Ile, Val, Glu, Asp, or Lys,

Xaa at position 33 is Val, Gly, Ala, Ser, Thr, Leu, Ile, Glu, Asp, or Lys,

Xaa at position 34 is Lys, Arg, Glu, Asp, or His,

Xaa at position 35 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 36 is Arg, Lys, Glu, Asp, or His,

Xaa at position 37 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys, or is deleted,

Xaa at position 38 is Arg, Lys, Glu, Asp, or His, or is deleted,

Xaa at position 39 is Arg, Lys, Glu, Asp, or His, or is deleted,

Xaa at position 40 is Asp, Glu, or Lys, or is deleted,

Xaa at position 41 is Phe, Trp, Tyr, Glu, Asp, or Lys, or is deleted,

Xaa at position 42 is Pro, Lys, Glu, or Asp, or is deleted,

Xaa at position 43 is Glu, Asp, or Lys, or is deleted,

Xaa at position 44 is Glu, Asp, or Lys, or is deleted, and

Xaa at position 45 is Val, Glu, Asp, or Lys, or is deleted, or

(a) a C_{1-6}-ester thereof,

(b) an amide, C_{1-6}-alkylamide, or C_{1-6}-dialkylamide thereof; or

(c) a pharmaceutically acceptable salt thereof,

provided that

(i) when the amino acid at position 37, 38, 39, 40, 41, 42, 43 or 44 of formula II is deleted, then each amino acid downstream of the amino acid is also deleted.

27. (Cancelled)

28. (Currently Amended) The method according to claim 26, wherein said GLP-1 agonist is selected from the group consisting of Arg^{26}, Lys^{34}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37), Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37), ~~exendin-3, exendin-4,~~ Val^{8}-GLP-1(7-37), Thr^{8}- GLP-1(7-37), Met^{8}- GLP-1(7-37), and Gly^{8}-GLP-1(7-37).

29 (Previously Presented) The method according to claim 26, wherein said GLP-1 agonist binds to a GLP-1 receptor with an affinity constant (Kd) below 1 μM.

Claims 30-35 (Cancelled).

36. (Previously Presented) The method according to claim 26, wherein said patient suffers from a disease state that is alleviated by lowering serum levels of said one or more lipids.

Claims 37-42 (Cancelled)

43. (Previously Presented) The method according to claim 26, wherein the GLP-1 agonist is GLP-1 (7-37) or GLP-1 (7-36) amide.

44. (Previously Presented) The method according to claim 26, wherein the GLP-1 agonist is an analogue of GLP-1 (7-37).

45. (Previously Presented) The method according to claim 44, wherein in the analogue of GLP-1 (7-37), one amino acid residue of GLP-1 (7-37) has been substituted by another amino acid residue.

46. (Previously Presented) The method according to claim 26, wherein the GLP-1 agonist is a derivative of GLP-1 (7-37).

47. (Previously Presented) The method according to claim 46, wherein the derivative of GLP-1 (7-37) has one or more lipophilic substituents.

48. (Previously Presented) The method according to claim 46, wherein the derivative of GLP-1 (7-37) is a derivative of an analogue of GLP-1 (7-37).

49. (Previously Presented) The method according to claim 48, wherein in the analogue of GLP-1 (7-37), one amino acid residue of GLP-1 (7-37) has been substituted by another amino acid residue.

50. (Previously Presented) The method according to claim 49, wherein the derivative is Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37).

Claims 51-72 (Cancelled)

73. (Currently Amended) ~~A~~ The method of claim 1, wherein the method is for lowering triglycerides in a patient~~, said method comprising administering to a patient~~ in need thereof ~~lowering of saidtriglycerides a GLP-1 agonist in an amount effect to lower said triglycerides, wherein said GLP-1 agonist is selected from the group consisting of GLP-1 (7-37), GLP-1 (7-36) amide, exendin-3, exendin-4, or an analogue or derivative of any of the foregoing~~.

74. (Currently Amended) The method according to claim 73, wherein said GLP-1 agonist is selected from the group consisting of Arg^{26}, Lys^{34}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37), $Arg^{~~34~~34}$,$Lys^{26~~26~~}$(N-εε-(γγ-Glu(N-αα-hexadecanoyl)))-GLP-1(7-37), ~~exendin-3, exendin-4,~~ Val^{8}-GLP-1(7-37), Thr^{8}- GLP-1(7-37), Met^{8}- GLP-1(7-37), and Gly^{8}-GLP-1(7-37).

75. (Previously Presented) The method according to claim 74, wherein said GLP-1 agonist is selected from the group consisting of Arg^{26},Lys^{34}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37).

76. (Previously Presented) The method according to claim 73, wherein said GLP-1 agonist binds to a GLP-1 receptor with an affinity constant (Kd) below 1 μM.

77. (New) The method according to claim 26, wherein the method is for lowering free fatty acids in a patient in need thereof.

78. (New) The method according to claim 77, wherein said GLP-1 agonist is selected from the group consisting of Arg^{26}, Lys^{34}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37), Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37), Val^{8}-GLP-1(7-37), Thr^{8}- GLP-1(7-37), Met^{8}- GLP-1(7-37), and Gly^{8}-GLP-1(7-37).

79. (New) The method according to claim 78, wherein the derivative is Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37).

80. (New) The method according to claim 77, wherein said GLP-1 agonist binds to a GLP-1 receptor with an affinity constant (Kd) below 1 μM.